



PATENT

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In re	: Application of	: Group Art Unit 1616
	: T. Zhang	: Examiner: J. Pak
Appln. No.	: 08/702,011	:
Filed	: August 23, 1996	:
For	: AN INJECTABLE	: Attorney Docket
	: COMPOSITION FOR CANCER	: No.: 3129-4000
	: TREATMENT	:

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION OF GUO-QIANG CHEN, M.D., Ph.D. UNDER 37 C.F.R. § 1.132

I, Guo-Qiang Chen, M.D., Ph.D., declare that:

1. I am a physician-scientist currently studying the use of arsenic trioxide to treat blood cancers, especially acute promyelocytic leukemia (APL).
2. I received a B.S. in Medicine from Hengyang Medical College in 1985; an M.S. in Pathophysiology at Shanghai Second Medical University in China in 1988; and an M.D./Ph.D. in Hematology at Shanghai Second Medical University in 1996.
3. I am presently an Associate Professor and Vice-Director of the Department of Biology at the Institute of Hematology of Rui-Jin Hospital; a Vice-Director of the Department of Biology at Shanghai Second Medical University; and a Visiting Research Assistant Professor at the Mount Sinai School of Medicine in New York. I have been studying and working in the scientific and/or medical field for almost 20 years.
4. During my career, I have received the following awards and honors: (1) the 1996 Award for Outstanding Young Scientific Phosphor of Shanghai Municipality; (2) the 1997

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Award for Outstanding Young Scientist from the National Natural Sciences Foundation of China; and (3) the 1997 First Degree Award for the Progress in Sciences and Technologies of Shanghai Municipality.

5. I have authored and co-authored many scientific publications relating to the use of arsenic compounds for the treatment of APL in various journals. Some of these publications include: (1) Chen et al., In vitro studies on cellular and molecular mechanisms of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia: As_2O_3 induces NB4 cell apoptosis with down-regulation of Bcl-2 expression and modulation of PML-RARA/PML Protein. *Blood* 1996; 88:2025; (2) Chen et al., Pharmacokinetics and efficacy of low-dose all-trans retinoic acid in the treatment of acute promyelocytic leukemia. *Leukemia* 1996; 10: 825; and (3) Su-Yin Zhang et al., Establishment of a human acute promyelocytic leukemia-ascites model in SCID mice. *Blood* 1996; 87: 3404.

6. I am familiar with the subject matter of the above-referenced patent application, which teaches pure arsenic trioxide being administered intravenously to treat APL. I further understand that the claims of the application have been rejected under 35 U.S.C. § 103 on the grounds of obviousness largely in view of the Sun et al. reference titled, "Use of Ai-Ling No.1 injection combined with pattern identification theory of Chinese traditional medicine, in the treatment of acute promyelocytic leukemia: Report from 32 patients."

7. At the Shanghai Institute of Hematology at Rui-Jin Hospital and Shanghai Second Medical University, where I am a Professor, we have received international recognition for a series of achievements, including the discovery of all-trans retinoic acid as a treatment for leukemia. During the past six years, I have directed bedside and bench studies on the use of arsenic trioxide (AT) to treat blood cancers, especially acute promyelocytic leukemia (APL). Actually, I was the responsible author of the August, 1996 publication in the journal, *Blood*, that made AT attract worldwide interest for cancer therapy. Therefore, I believe that I understand clearly the history and recent progress on the application of AT in the treatment of APL. In addition, I am familiar with Dr. Tingdong Zhang and his experimentation and teachings on the treatment of APL.

8. In the early 1970's when China was in the so-called "Cultural Great Revolution,"

many doctors were recalled into the countryside to provide medical services for farmers. As a director of such a team, Dr. Zhang of Harbin Medical University found that some rural doctors used "xinshi" (arsenic stone in English) and herbal concentrates to treat some cancers; some indefinite effectiveness in such treatment was demonstrated. Thereafter, Dr. Zhang and his colleagues returned to study the use of AT to treat cancers.

9. First, Dr. Zhang and his colleagues prepared a solution called "Ai-Ling No. 1" (meaning in Chinese "the most effective drug for treatment of cancers"), which were crude extracts at least containing arsenic stone or arsenic sublimate and HgCl. With about 20 years of experimentation, they published the first short report in the Chinese Journal of Integration of Chinese and Western Medicine in 1992 (the Sun et al. reference). In this paper, they showed that Ai-Ling No. 1 combined with other Chinese herbs, such as Ginseng White Tiger Decoction and others, induced cancer remission in 21 of 32 APL patients. The specific role of arsenic still remained unknown. Subsequent studies showed that the HgCl component has little value other than increasing the toxicity of this treatment. Therefore, Dr. Zhang began to change the composition of Ai-Ling No. 1. In early 1996, he first reported in the Chinese Journal of Hematology that intravenous infusion of pure arsenic trioxide could effectively treat APL. Zhang was awarded a Chinese patent in 1999 for that discovery, from a patent application corresponding to the above-referenced application.

10. It should be emphasized that the original Ai-Ling No. 1 formulation is different from the currently used drug, pure arsenic trioxide. According to the Chinese Drug Dictionary, Xin-shi, the main composite of Ai-Ling No. 1, is a mixture of arsenolium and arsenopyritum. This is mainly composed of As₄O₆ mixed with ferric and sulfite. At the time of Dr. Zhang's invention, Xin-Shi was considered to be toxic and was used only in topical form. Therefore, in my professional opinion, the prevalent teaching at that time, including the Sun et al. reference, was not to develop and use arsenic in any form without additives, but to administer it along with detoxifying herbs.

11. Dr. Zhang's development of pure arsenic trioxide went against the teaching in the prior art at that time in China and elsewhere. Although Ai-Ling No. 1, with the herbal concentrates, was effective in treating APL at least as early as 1992, it was not clear what the

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active ingredient was. Thus, in my professional opinion, there was no motivation at that time to use a pure form of arsenic without Chinese herbs/additives for the intravenous treatment of APL. In the face of the conventional wisdom at that time, Dr. Zhang is credited with the discovery of such an intravenous use of arsenic trioxide.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

01/03/01
Date

Cheng Qiang Zhang
Guo-Qiang Cheng, M.D., Ph.D.